Exhibit 12

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/380,696	11/29/99	LO Y	SHP-PT048

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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	12

DATE MAILED: 11/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

U.S. G.P.O. 2000 ; 465-188/25266

Office Action Summary	Application No.	Applicant(s)	
	09/380,696	LO ET AL.	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *22 September 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. This action is in response to the papers filed September 22, 2000. Currently, claims 1-28 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Priority

3. This application is a 371 of GB98/00690, filed March 4, 1998. This application also claims priority to GB9704444, filed March 4, 1997. However, claims 7-8, 17, 20-21, and 24 are not supported by GB9704444. Claims 7-8 are not supported by the GB9704444 document because although the document discloses sex determination and other polymorphisms which are present in the father, but not the mother, the disclosure does not describe either detecting DYS14 locus nor the SRY gene. Claim 17 is directed to variations of fetal DNA concentrations over the different stages of gestation, however, no mention of this difference was disclosed in the Great Britain document. Claims 20-21 are directed to specific concentrations of fetal DNA, which were not disclosed in the foreign priority document. Although the document discloses that "another potential application is the quantification of fetal nucleic acid in maternal serum or plasma", no specifics were provided (pg. 5). Finally, Claim 24 is not supported by the foreign document because no mention of clotting to extract serum and plasma is

provided. Therefore, Claims 7-8, 17, 20-21, and 24 receive benefit of the GB98/00690 application filed March 4, 1999.

Response to Arguments

The response traverses the rejection. The response asserts that Claim 7 and 17 are supported by the specification of GB9704444, filed March 4, 1997, and thus should receive priority. This argument has been reviewed. With respect to Claim 7, the examiner acknowledges the document does refer to DYS14 and agrees that Claim 7 should receive benefit of March 1997.

However, with regards to Claim 17, the response asserts that the GB9704444, filed March 4, 1997 supports variations of fetal DNA concentrations over the different stages of gestation. The response states that "on skilled in the art would have also been aware that fetal DNA generally shows a variation over the course of a pregnancy. Further, the response states that "it would be desirable to make a comparison with a sample from a similar stage of gestation". This argument has been reviewed, but is not convincing because the priority document states "detection and monitoring of pregnancy-associated conditions such as pre-eclampsia which may result in differing amounts of foetal DNA being present in the maternal serum or plasma" (pg. 2, lines 24-27). This statement while proposing that variation occurs, does not provide any specific evidence that variations in fact exist, nor provides the variations from normal as stated in Claim 17. Secondly, based upon the inventive nature presumed for the invention, the skilled artisan would not have been aware that fetal DNA existed in the serum/plasma, and thus would not have "been aware that foetal DNA shows a variation over the course

of pregnancy". Finally, it is acknowledged that "a comparison" would be desirable, however, the comparison was not performed in the foreign document.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of paternally inherited fetal DNA in maternal plasma after 15 weeks of gestation wherein the fetal DNA is from the Y chromosome and for detecting the presence of the RhD gene in maternal plasma from an RhD negative pregnant women after 15 weeks gestation, does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general at any time during pregnancy or associated with disease phenotype in serum. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to us the invention commensurate in scope with these claims.

The claims are broadly drawn to a detection method performed on serum or plasma of a pregnant woman to detect any fetal DNA at any point in pregnancy.

The specification teaches fetal DNA has been detected in both serum and plasma. Table 2 and 3 show the quantification of fetal DNA in maternal serum and plasma in relation to the gestational age (pg. 33). The specifications teaches the

detection of the Y-chromosome by markers to DYS14 locus and SRY gene. The specification teaches that plasma and serum samples were collected from 43 pregnant women with gestational ages from 12 to 40 weeks (pg. 9, para. 1). Of the 30 male fetuses, detection of a Y-positive signal occurred in 24 plasma samples and only 21 serum samples (pg. 9,para. 1). The specification also teaches a RhD status determination from plasma of RhD-negative pregnant women (pg. 15 and Table 1, pg. 20).

The art teaches unpredictability in detecting fetal DNA in plasma before the 15th week of gestation, of detecting paternally inherited non-Y sequences, and the unpredictability of detecting fetal DNA in serum samples. Specifically, Lo et al (New England J. of Med. , Vol. 339, No. 24, pages 1734-8, December 1998) teaches reliable results for fetal RhD status determination were obtainable from the 15th week of gestation and beyond in RhD negative women. Lo teaches that 7 of 9 fetus were positive on PCR testing for RhD genotyping (Table 1, pg. 1736). Lo teaches that two women with gestation ages of eight and nine weeks yielded false negative results (pg. 1735, col. 2, para. 6). Lo explicitly states "our data suggests that results of the RhD PCR test are reliable beginning in the second trimester" (pg. 1736, col. 2, para. 2). Additionally, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) teaches "it is likely that future improvements in technology may allow more accurate diagnosis to be made and potentially extend the applicability of this method to the first trimester of pregnancy" (pg. 310, col. 2, para. 1) suggesting that the technology does not currently

exist and may not have been conceived of as of yet what would be required to diagnose in the first trimester.

Moreover, the art teaches the detection of fetal DNA in maternal plasma for an expanded CGT trinucleotide repeats, in the DM kinase gene on chromosome 19, in the range of 50-4000 repeats (Amicucci et al, February 2000, Clinical Chemistry, Vol. 46, No. 2, pages 301-302). Amicucci teaches sampling of plasma from pregnant women at 10 weeks of gestation to detect the expanded repeat present only in the father. Amicucci states "at present, this test seems appropriate only for monitoring paternally inherited expanded alleles" (pg. 302, para. 2). Additionally, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) states "the success of the detection of fetal-derived RhD gene in the plasma and serum of pregnant women opens up the possibility that a similar approach may be used for other single-gene disorders" (pg. 310, col. 2, para. 3). However, Lo has not taught single gene disorders other than RhD which may in fact use this technique. Furthermore, the RhD analysis was only shown to be successful on RhD-negative women. The language of the paper is that of suggestion, and hypothesis rather than of evidence that this method works for these suggested single-gene disorders.

Furthermore, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) teaches increase amount of maternal DNA have been found in serum when compared with plasma (pg. 310, col. 1, para. 3). Further, the results "indicated that a higher maternal background is present when serum is used which may be detrimental for the detection of fetal DNA, especially when less sensitive detection methods are used"(pg.

310, col. 1, para. 3). Bianchi (Am. J. Hum. Genetics, Vol. 62, pg. 763-764, April 1998) teaches that the fractional concentration of fetal nucleic acid in serum was significantly less because of the increased amount of total DNA in serum (pg. 763, col. 1, para. 3). Bianchi moreover teaches that these results validate the results of Lo which showed that fetal DNA would be reliably detected in as little of 10 microliters of maternal plasma. Furthermore, Bianchi states that "although fetal aneuploidy might be suggested by increased amounts of fetal DNA present in maternal plasma, cytogenetic confirmation using intact nuclei will ultimately be necessary (pg. 764, col. 1, para. 3). Bischoff et al (J. of the Society for Gynecologic Investigation, Vol. 6, No. 2, pages 64-69, Mar-April 1999) teaches detection of RhD in serum. However, Bischoff teaches that "our less than 100% detection efficiency probably reflects serum DNA purity, variable fetal DNA concentration in maternal serum, and DNA degradation caused by freezing and thawing of the serum samples" (pg. 67, col. 1).

Neither the specification nor the art provide guidance to overcome the unpredictability of detecting fetal DNA in plasma before the 15th week of gestation, of detecting paternally inherited non-Y sequences, and the unpredictability of detecting fetal DNA in serum samples. It would require undue experimentation for the ordinary artisan to practice the invention as broadly as claimed. The concentration of fetal DNA in maternal plasma at early stages of gestation appears to be low. Thus predictably detecting fetal DNA in maternal plasma samples before the 15th week of gestation is unpredictable and would require the ordinary artisan to enrich the fetal DNA in some manner which have not been described. In addition clinical studies would be required to

determine the level of sensitivity of detection of paternally inherited sequences. Since, Amicucci explicitly states in his work as of February 2000, "at present, this test seems appropriate only for monitoring paternally inherited expanded alleles" (pg. 302, para. 2), it appears the sensitivity of the method can only detect huge expansions. Thus, detection of all paternally inherited non-Y sequences would be unpredictable. While, the detection of paternally inherited non-Y sequences includes huge expansions, detection of single gene mutations which differed from mother to father, translocations, deletions would be unpredictable. Finally, the detection of fetal DNA in serum appears unpredictable based upon the teachings by Lo that the results "indicated that a higher maternal background is present when serum is used which may be detrimental for the detection of fetal DNA, especially when less sensitive detection methods are used"(pg. 310, col. 1, para. 3). Thus, the above analysis demonstrates that the skilled artisan would be required to perform undue experimentation to make and use the invention as claimed.

Response to Arguments

The response traverses the rejection. The response asserts that specification is enabling across the scope of the breadth of the claim for detection method over the course of pregnancy. The response asserts that "the paper demonstrates that testing prior to 15 weeks of gestation is already useful". This argument has been reviewed but is not convincing because the art teaches that "noninvasive fetal RhD genotyping can be performed rapidly and reliably with the use of maternal plasma beginning in the second trimester of pregnancy" (abstract). The paper teaches that "plasma samples

from two women in the first trimester of pregnancy who were carrying RhD-positive fetuses, with gestational ages of eight and nine weeks, yielded false negative results". The paper explains "the results for the two first-trimester samples which were false negative, presumably because of the low concentration of fetal DNA in maternal plasma at that time" (pg. 1736, col. 2). The paper illustrates that amplification is required for sensitivity of the PCR analysis for the detection of RhD DNA, such that with 25 or fewer amplification cycles showed no intensity of fluorescence of study (Figure 1). The paper also illustrates that different weeks of gestation are detectable after different numbers of cycling (Figure 2). The teachings in the specification support these results such that the concentration of SRY in early pregnancy and late pregnancy differ substantially. For example, in early pregnancy plasma an average of 25.4 copies/ml are found while 292.2 copies/ml are found in late pregnancy. Similarly, in early pregnancy serum an average of 28.7 copies/ml are found while 342.1 copies/ml are found in late pregnancy. Which adds to the unpredictability of detecting fetal DNA in maternal serum/plasma prior 15 weeks of gestation and without any amplification.

Secondly, the response asserts that the comments found in Lo et al (Annals of Medicine, Vol. 31, No. 5, pg. 308-312, 1999) regarding applicability of the method for the first trimester, is not to say that the techniques can not be sued as a diagnostic method across the scope of the claims. This argument has been reviewed but is not convincing because the reference was cited to support the position that predictable detection prior to 15 weeks of gestation is unpredictable. The statement by Lo "it is likely that future improvements in technology may allow more accurate diagnosis to be

made and potentially extend the applicability of this method to the first trimester of pregnancy" indicates that currently the method is not applicable for the first trimester and even with the technological improvements, the accurate detection within the first trimester is unpredictable.

Thirdly, the response asserts that the statement that PCR tests are reliable beginning in the second trimester does not say that such tests can not be useful when carried out before the second trimester. This argument has been reviewed but is not convincing because the problem of detection prior to the second trimester appears to be sensitivity. The instant claims are not directed to a PCR or amplification method such that this step is required. Nevertheless, if the problem as stated by Lo et al (New England J. of Medicine) is detection of low concentration, it is likely that method contains false negatives. The response appears to be discussing false positives in which a "potential problem" may be highlighted. However, it seems as though the lack of detection of the nucleic acid would present more of a problem leading to the unpredictability. With regard to the three articles cited in the response that support the detection in the first trimester, each of these articles require that an amplification step is performed such that this detection is plausible, such that it appears that an amplification step is a critical feature of the invention. Smid provides different amplifications and illustrates that false-positive results occur.

In conclusion, based upon the remarks and arguments presented, it remains unpredictable to detect the presence of a nucleic acid of foetal origin in the sample prior to 15 weeks of gestation as provided above. Further, the claims remain broadly drawn

to the detection of nucleic acids of fetal origin, however, the detection of a maternally inherited nucleic acid from the fetus is unpredictable. The specification explicitly states that "the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother" (pg. 4, lines 5-7). As stated in numerous of the papers the concentrations of fetal DNA in maternal plasma may reach 3.4% in early pregnancy and 6.2% in late pregnancy, however, there is a much higher percentage of maternal DNA in the plasma. Provided that the skilled artisan obtained a positive result for detection of the nucleic acid, it would require undue experimentation determine whether the nucleic acid was a results of the maternal DNA found in the maternal plasma or whether in fact the nucleic acid was from the fetus. Thus, detection of a maternally inherited nucleic acid would be unpredictable and require undue experimentation.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claim 17 is rejected under 35 U.S.C. 102(a) as being anticipated by Lo (Lancet, August 1997).

It is noted that the authorship of the Lo et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration. This rejection applies to the claims because as discussed previously this claim does not have foreign priority to the March 4, 1997 British patent application.

Lo et al. (herein referred to as Lo) teaches the detection of fetal DNA in maternal plasma and serum (abstract). Lo further teaches the detection of DYS14 from the Y chromosome (pg. 486, col. 1, para. 2)(limitations of Claim 7). Lo teaches that fetal DNA increases as gestation progresses (pg. 487, col. 1, para. 3)(limitations of Claim 17).

Response to Arguments

The response traverses the rejection. The response asserts that priority should be granted a discussed above in the priority section and thus the rejection is not applicable. This argument has been reviewed but is not convincing because the priority document does not support all of the claims. The priority document states "detection and monitoring of pregnancy-associated conditions such as pre-eclampsia which may result in differing amounts of foetal DNA being present in the maternal serum or plasma" (pg. 2, lines 24-27). This statement which proposing that variation occurs, does not provide any specific evidence that variations in fact exist, nor provides the variations from normal as stated in Claim 17. Secondly, based upon the inventive nature presumed for the invention, the skilled artisan would not have been aware that fetal DNA existed in the serum/plasma, and thus would not have "been aware that foetal DNA shows a variation over the course of pregnancy". Finally, it is acknowledged that

"a comparison" would be desirable, however, the comparison was not performed in the foreign document.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No Claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
November 1, 2000

W. Gary Jones
Supervisory Patent Examiner
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11/1/00